

## Food and Nutrition Report

# Does the Existence of Senolytic Compounds Underpin that Anti-Senolytics May Exist? A View on the Heaven and Hell of Cellular Senescence

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### Abstract

The discovery of compounds that can selectively target senescent cells (called senolytic compounds) has moved lot of research around this new field of development of drugs and nutraceutical compounds. The promises, expectations and innovations in the therapy of age-related pathologies characterized by an increased low grade chronic inflammatory status [which is likely driven in part by the senescence-associated secretory phenotype (SASP) produced by accumulating senescent cells] are so high that we are tempted to describe this field as a new scientific “Heaven”. However, if this Heaven is real, that might seem to suggest that Hell is also real. In this case the term “Hell” refers not only to the potential side-effects of senolytic compounds and to the pro-senescence effects displayed by other compounds, but also to the possibility that real “anti-senolytics” exist. We cannot exclude that among common drugs (in particular those associated with chronic side-effects in elderly) or natural bioactive compounds there are molecules able to promote resistance to apoptosis in senescent cells, or able to depress senescence immune surveillance thus promoting accumulation of senescent cells. Comparing differential effects of drugs and bioactive compounds in senescent versus normal cells could ameliorate the development of drugs and nutraceuticals tailored to the needs of elderly people.

**Keywords:** Cellular senescence, Senolytics, Immune surveillance, Senescent cells.

### Introduction

In the last two years a new term has been introduced in scientific literature: “senolytic agents” (or “senolytic compounds”). This term was coined to describe natural or synthetic compounds that can selectively kill senescent cells without any dramatic effect on normal proliferating and terminally differentiated cells [1]. The discovery that a common anticancer drug, dasatinib, and a well-known flavonol, quercetin, can display senolytic activity on senescent pre-adipocytes and endothelial cells, respectively,

was immediately followed by the discovery of additional senolytic compounds, thus reinforcing the idea that this could be a complete new field of development of drugs and nutraceutical compounds. Most of these compounds appears to act as inhibitors of Bcl-2 family member proteins. ABT263 (a specific inhibitor of the antiapoptotic proteins Bcl-2 and Bcl-xL), can induce apoptosis in various senescent cells, including senescent bone marrow hematopoietic stem cells and senescent muscle cells [2]. Navitoclax, which targets Bcl-2, Bcl-xL, and Bcl-w, was shown to be senolytic for senescent endothelial cells and fibroblasts [1]. Other mechanisms on the basis of senolytic activity include the inhibition of glucose metabolism (e.g. byphloretin) and of the protein degradation pathways that have been found up regulated in various models of senescent cells [3]. Several other compounds, including natural bioactive compounds, have the potential to display senolytic activity thus raising the interest for the development of a new class of nutraceuticals. Reasonable senolytic candidates among nutritional compounds are those molecules displaying rejuvenating effects on senescent cells “in vitro”, as this effect might be the consequence of the senolytic activity combined with a selective survival of a sub-population of non-senescent cells in the culture [4,5].

### Rationale for the “Senolytic Heaven”

Although it is well recognized that cellular senescence is a beneficial phenomenon in the organism as a defense against cancer as well as in wound healing [6], control of fibrosis and tissue repair [7], the proper use of compounds that can remove excessive accumulation of senescent cells appears beneficial as well. Senescent cells display a particular chromatin configuration that stably silence proliferation-promoting genes while simultaneously activates the SASP program. One of the functions attributed to the SASP is to attract immune cells, which in turn can coordinate the elimination of senescent cells. However, the SASP is suspected to promote aged phenotype of tissues as well as chronic inflammation and even the development of a pro-tumorigenic microenvironment [8].

The rationale under the development of senolytic compounds lies in the concept that senescent cells accumulate excessively in organs and tissues during aging, thus contributing to the physiological decline and pathological changes [9–11]. These observations have led to the idea that physiological mechanisms that are deputed to the clearance of senescent cells can be affected by aging. The age-associated alterations of the immune system can contribute to impair the organism's ability to clear-off senescent cells. Moreover, there is also evidence that most senescent cells can develop resistance to apoptosis, so that some researchers are currently considering them like “non-proliferating cancers”. This fact may be consequent to epigenetic changes occurring in cells during individual life span that cause intrinsic modifications in senescent cells, leading to phenotypic diversification and selection of senescent cells resistant to immune system clearance [12]. Most importantly, genetic based strategies to remove the excesses of senescent cells from the organism have been proven to rejuvenate tissues and extend lifespan in laboratory mice [13,14]. These beneficial results have been also confirmed with the administration of senolytic compound in murine models “in vivo” [1,2,15].

### Hypothesis on the “Anti-Senolytics Hell”

Based on this concept, lots of studies are currently under way looking at cellular senescence as an innovative target for the major diseases and chronic conditions associated with aging. This new field of research promises expectations and innovations in the therapy of sarcopenia, type 2 diabetes, immune system decline and cardiovascular diseases as well as in all age-related pathologies characterized by an increased low grade chronic inflammatory status (which is likely driven in part by the SASP produced by accumulating senescent cells). The enthusiasm expressed around the development of senolytic compounds is quite like the discovery of a scientific “Heaven”. However, if this Heaven is real, that might seem to suggest that Hell is also real. In this case the term “Hell” refers to those negative implications that arise from the concept that “compounds that eliminate accumulating senescent cells are good”. The first of these inauspicious consideration is that side effects associated with certain drugs or bioactive compounds can arise from a promotion of accumulating senescent cells. For example, accelerated aging and long-term complications after cancer therapy are the likely consequence of extensive senescence induction in off-targets healthy cells [16]. However, there are several other compounds which display side effects likely associated to induction of senescence. Very recently, accelerated endothelial senescence has been claimed as a potential mechanism to explain the cardiovascular, renal and neurological morbidity associated with proton pump inhibitors use [17]. The poor knowledge around effects on normal cells and potential side effects of senolytics also deserve particular care. Scientific research is currently in the stage of basic and pre-clinical testing of these compounds. It is necessary to urgently intensify the laboratory work “in vitro” as well as “pre-clinical” studies in laboratory mice in order to check potential senolytic activities of natural and synthetic compounds, as well as to verify their effects using models “in vivo”. Indeed, senolytic treatments may affect the beneficial role of senescent cells in tissue repair [12] and, importantly, there may be other unidentified advantageous effects of senescence, especially in humans [18]. Another lack of knowledge regards

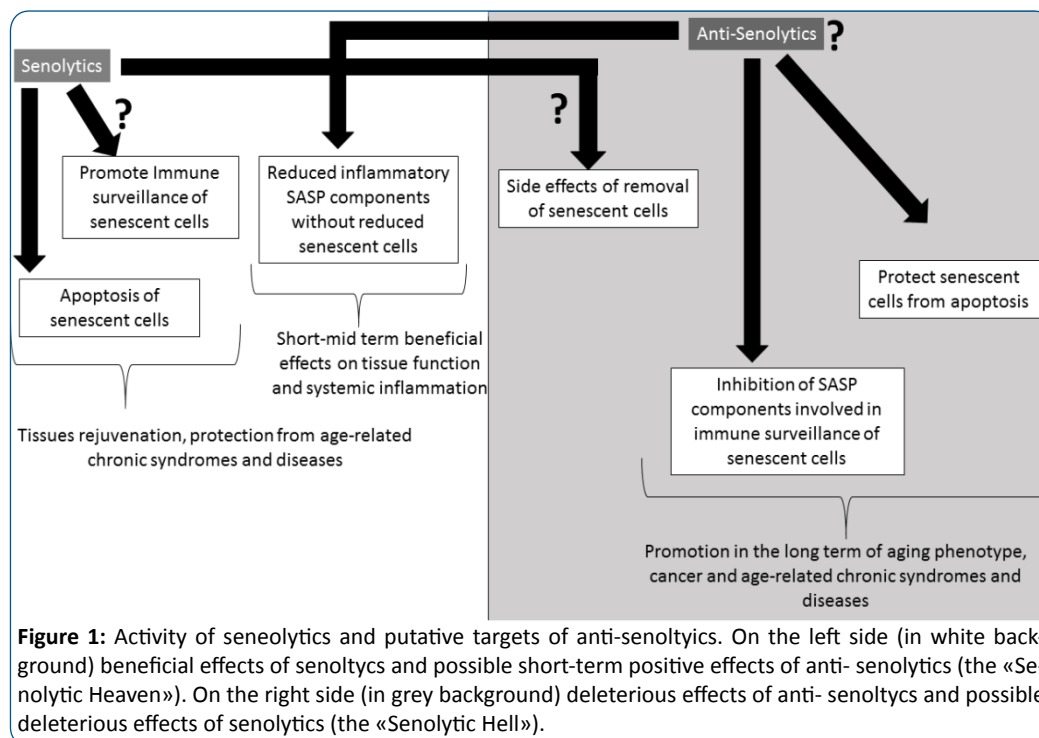
the possibility that certain drugs (in particular those associated with chronic or severe side-effects in elderly) or natural bioactive compounds may be able to protect senescent cells from apoptosis or, to depress senescence immune surveillance (“anti-senolytic” activity) thus promoting accumulation of senescent cells. These compounds may exert their activity by favoring the process of dysregulation of apoptotic pathways on newly formed senescent cells by a process similar to the one identified for volatile anesthetics and dexamethasone in certain cancer cellular models [19,20]. It has been shown that young and senescent cells can respond differently to treatment with cytokines (e.g. IFN- $\gamma$ ) [21], natural bioactive compounds (e.g. rotenone) [22], and common drugs (e.g. proton pump inhibitors) [17].

Some drugs (e.g. glucocorticoids), and natural bioactive compounds (e.g. resveratrol) have been studied for their capacity to decrease the production of SASP components in human senescent cells [23,24]. This effect generally consists of a reduced gene expression and release of pro-inflammatory cytokines, thus suggesting a potential beneficial improvement of tissue maintenance and repair. However, considering the original nature of SASP to attract immune cells for senescence immune surveillance, it would be important to of senescent cells thus hampering long term positive beneficial effects. In the case of glucocorticoids, this class of compounds may induce senescence [25], prevent apoptosis with mechanisms involving upregulation of Bcl-xL [26], suppress the SASP [27], and have been associated with immunosenescence [28], thus suggesting a deleterious impact on senescence immune surveillances. Hence, it would not be surprising to find out that part of side effects associated with long term use of glucocorticoids (e.g. in patients with asthma or chronic respiratory diseases) are the consequence of accumulating senescent cells. Additional pharmacological and nutritional compounds that can modulate the function of regulatory T (Treg) cells and myeloid derived suppressor cells (MDSCs) [29,30], could also play a role in suppression of immune surveillance of senescent cells. Unfortunately, there are still no focused studies in this area and the effects of long term administration of immunomodulatory compounds (including natural bioactive compounds and probiotics) in the accumulation of senescent cells are still unknown. It should be also mentioned that an high fat diet, which appears a likely candidate among nutritional anti-senolytics, was shown to not induce accumulation of senescent cells in the p16ink4a reporter mice [31].

In conclusion, given that senescent cells accumulate in old tissues, find out a possible anti-senolytic activity of drugs and natural bioactive compounds would be helpful to predict potential hazard of their long term use in elderly and even in younger people. A description of the mechanism that deserve particular attention in this field could be retrieved from Figure 1.

### Future Perspective

While most gene expression studies have been addressed to identify differences between normal and senescent cells, few studies have been focused to identify differences in gene expression response to drugs or natural bioactive compounds. There is urgent need to intensify these studies in order to ameliorate the development of drugs targeted to the need of elderly people. These studies should be flanked by others focused on the mechanisms



of accumulation of senescent cells “in vivo” using newly developed transgenic mouse models that allows to visualize, isolate and eliminate senescent cells [6] and including an important focus on senescence immune surveillance. Increasing knowledge around the mechanisms that drive accumulation of senescent cells during therapy may help scientists to ameliorate pharmacological and nutritional therapies in elderly.

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